Updates from ORD National Center for Environmental Assessment (NCEA) & Integrated Risk Information System (IRIS)

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EPA Science Advisory Board
August 29-30, 2017

NCEA's Assessments at EPA

NCEA's unique and essential role:

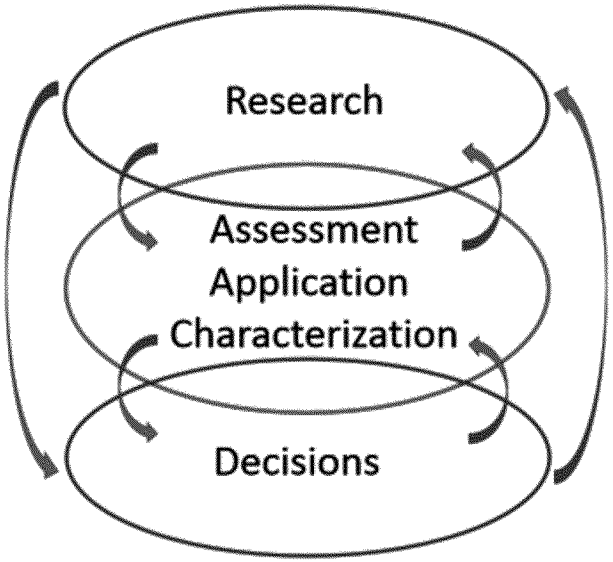
- Experienced and multi-disciplinary teams integrating and synthesizing findings from large bodies of evidence to develop scientific assessments
- Translating research and communicating scientific findings to inform Agency and State and local agency partner decisions

Critically positioned between:

- Researchers – inside and outside EPA -- who are generating new findings and data

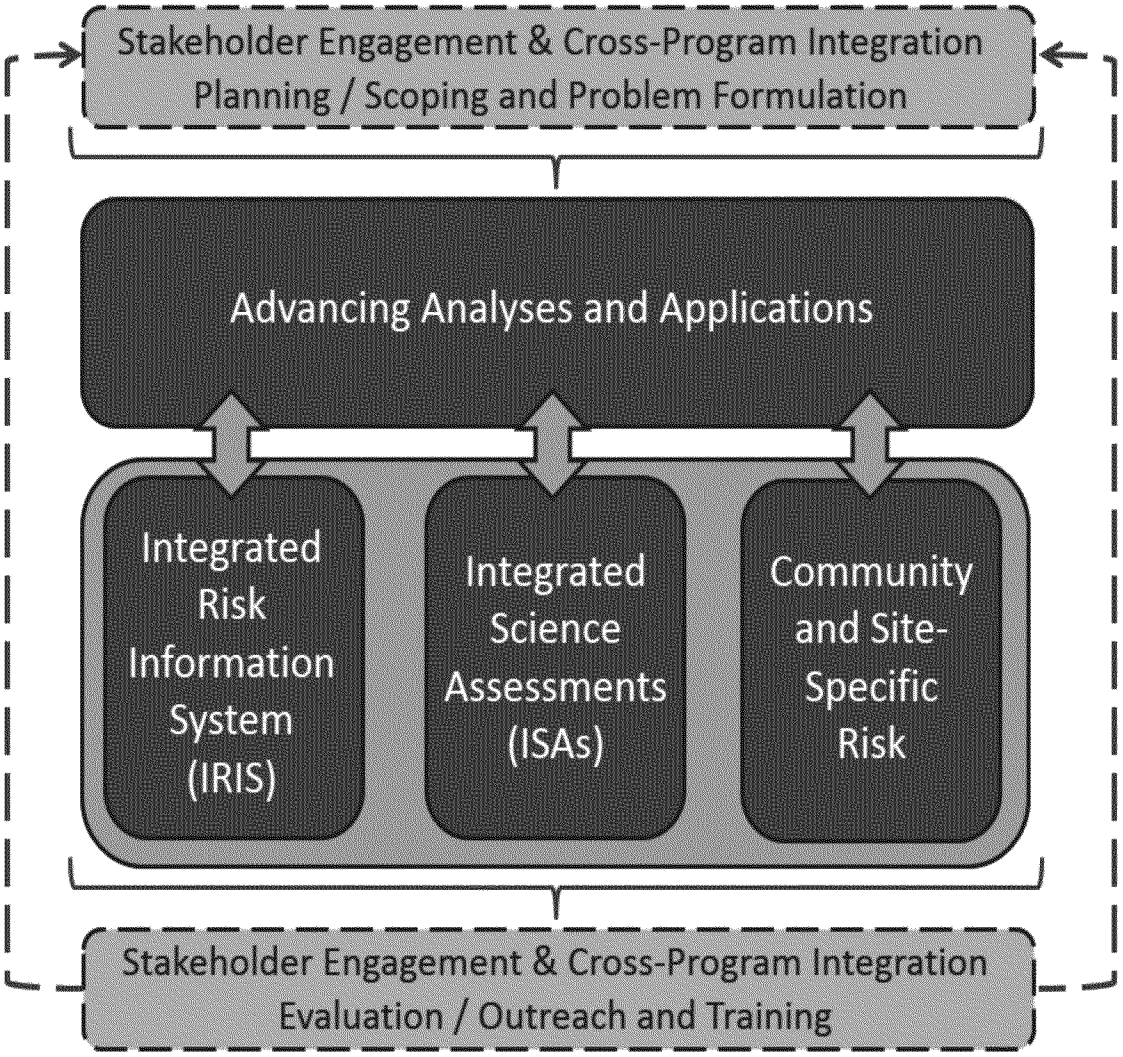
AND

- EPA Program and Regional offices, states and local agencies who must make regulatory, enforcement, and remedial actions and decisions



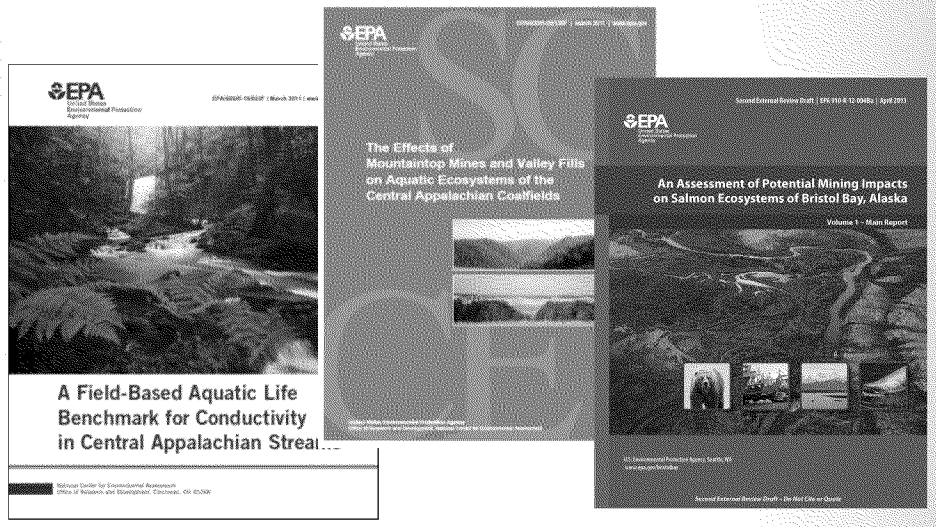
https://www.epa.gov/risk

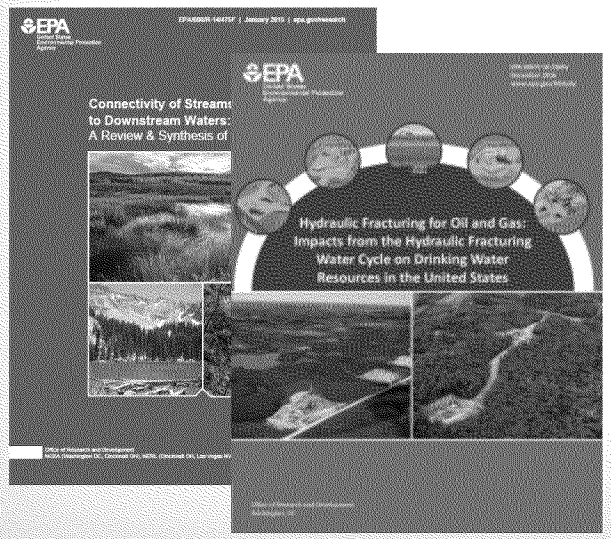
NCEA Human Health Risk Assessment



NCEA Environmental Assessments

- **High profile assessments support regulatory and policy decisions for Office of Water, Regions and States**
  - Support to OW & Regions to develop benchmarks for conductivity
  - Assessment of Mountaintop Mining that provided support for OW guidance and action under CWA 404(c)
  - Evaluation of potential impacts of large-scale mining activities on salmon resources in Bristol Bay, Alaska





- Connectivity of Waters of the United States: Synthesis of the scientific evidence on the connectivity of streams, wetlands, and open waters to downstream waters; scientific foundation for rulemaking to clarify CWA jurisdiction.
- Hydraulic Fracturing Drinking Water Assessment

NCEA continues to work with OW to translate science to effective policy, guidance, rules, and regulatory action.

New Leadership Structure in NCEA

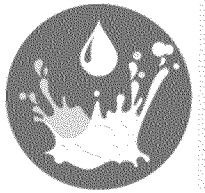
- **In January 2017, EPA appointed new leadership to the National Center for Environmental Assessment and to its IRIS Program.**
  - With significant experience in the chemical industry, and formerly the Director of ORD's Chemical Safety for Sustainability National Research Program, the new NCEA Director brings knowledge of TSCA, innovative applications of computational toxicology, and exposure science.
  - As a recognized leader in systematic review, automation, and chemical evaluations, the new IRIS Program Director brings experience in early partner and stakeholder engagement and input, and demonstrated actions to increase capacity and transparency in assessments.
- **Improved responsiveness and accountability through Senior Leadership Team**
  - NCEA IO
  - Divisions
  - Integrating across the spectrum of human and ecological RA practices

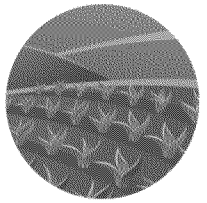
- Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.
- IRIS assessments contribute to decisions across EPA and other health agencies
- Toxicity values
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- IRIS is the only federal program to provide toxicity values for both cancer and noncancer effects.
- IRIS assessments have no direct regulatory impact until they are combined with
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options, which are the purview of EPA's program offices.

IRIS Addresses Agency Priorities and Mandates

IRIS

- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)



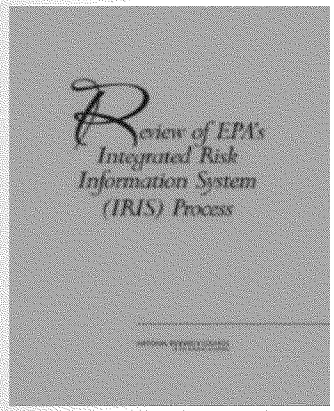


Broad Input to Support

- **Agency Strategic Goals**
- **Children's Health, Environmental Justice**

National Academy of Sciences (2014) Overarching Statements

2014



"Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made." [p.9]

" . . . the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process . . . Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]

Previous Phased Improvements to the IRIS Program

- The IRIS Program has taken prior, incremental steps to address the NAS recommendations, including:
- Revising the structure of assessments to enhance the clarity and transparency of presentation:
  - detailing the methods underlying each step of draft development (e.g., literature search strategy)
  - restructuring the document into separate hazard identification and dose-response chapters
  - replacing lengthy study summaries with synthesis text, supported by standardized tables and graphs
- Implementing "IRIS Enhancements", which laid out an updated process for developing and reviewing assessments that increases public input and peer consultation at earlier stages of assessment development, and clarifies processes for considering new evidence and scientific issues

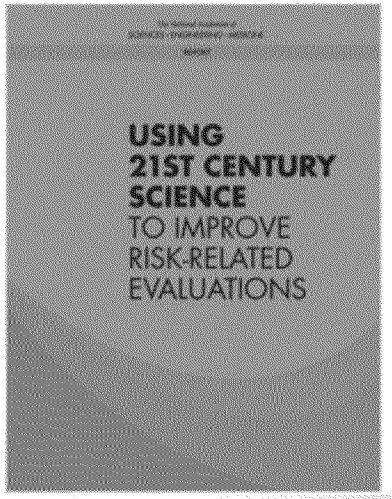
Previous Phased Improvements to the IRIS Program

- **Establishing the SAB Chemical Assessment Advisory Committee (CAAC) to strengthen peer review advice**
  - **5 IRIS assessments completed CAAC review since 2014**
- **Contracting with the NAS to arrange for independent experts to attend public meetings on science topics**
- **Restructuring the IRIS program to create expertise-specific workgroups and improved assessment oversight**

How is IRIS Focusing?

- **Increase transparency and full implementation of systematic review**
  - implement using approaches that foster consistency across the IRIS program; many active and all new starts address ALL SR-related recommendations of 2014 NRC report
- **Modernize the IRIS Program**
  - through automation and machine learning to expedite systematic review, incorporation of emerging data types
- **Modularize product lines**
  - implement a portfolio of chemical evaluation products that optimize the application of the best available science and technology. These products will allow IRIS to remain flexible and responsive to clients within the EPA as well the diverse collection of stakeholders beyond EPA, including states, tribal nations, and other federal agencies.
- **Enhance accessibility**
  - provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.

Other IRIS Improvements



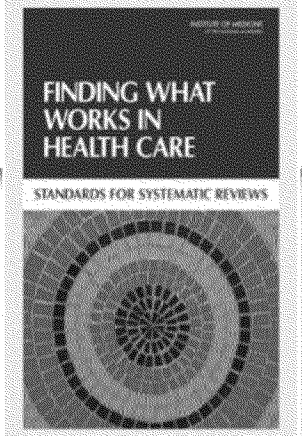
Next Generation IRIS

- IRIS in the 21st Century – implement recommendations of the NAS 2017 report, Using 21st Century Science to Improve Risk-Related Evaluations;
- Collaborate with EPA's National Center for Computational Toxicology (NCCT) to build expert-judgement case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals; inform where resources should be strategically invested to generate additional data.

Improved Management Practices

- Create efficiencies – engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- Improve timeliness and responsiveness – deploy program and project management tools to more effectively and efficiently utilize human resources to ensure timely delivery of products.

Systematic Review



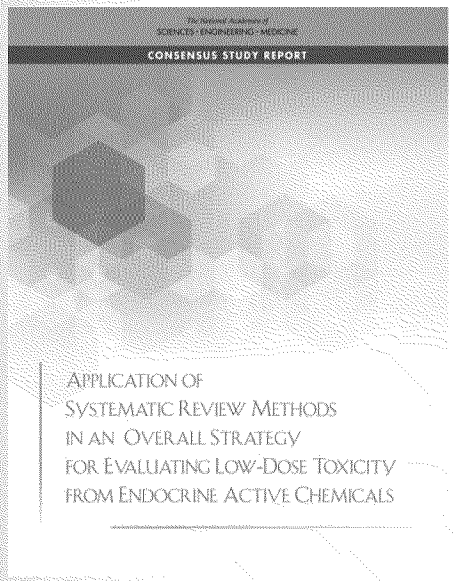
A structured and documented process for transparent literature review[1,2]

"… systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent"

[1] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654. https://www.epa.gov/sites/production/files/2017-06/documents/prepubcopy_tsca_riskeval_final_rule_2017-06-22.pdf

[2] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

NAS (2017): Reflections and Lessons Learned from the Systematic Review



"….one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review." [p.157]

"The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors." [p.157]

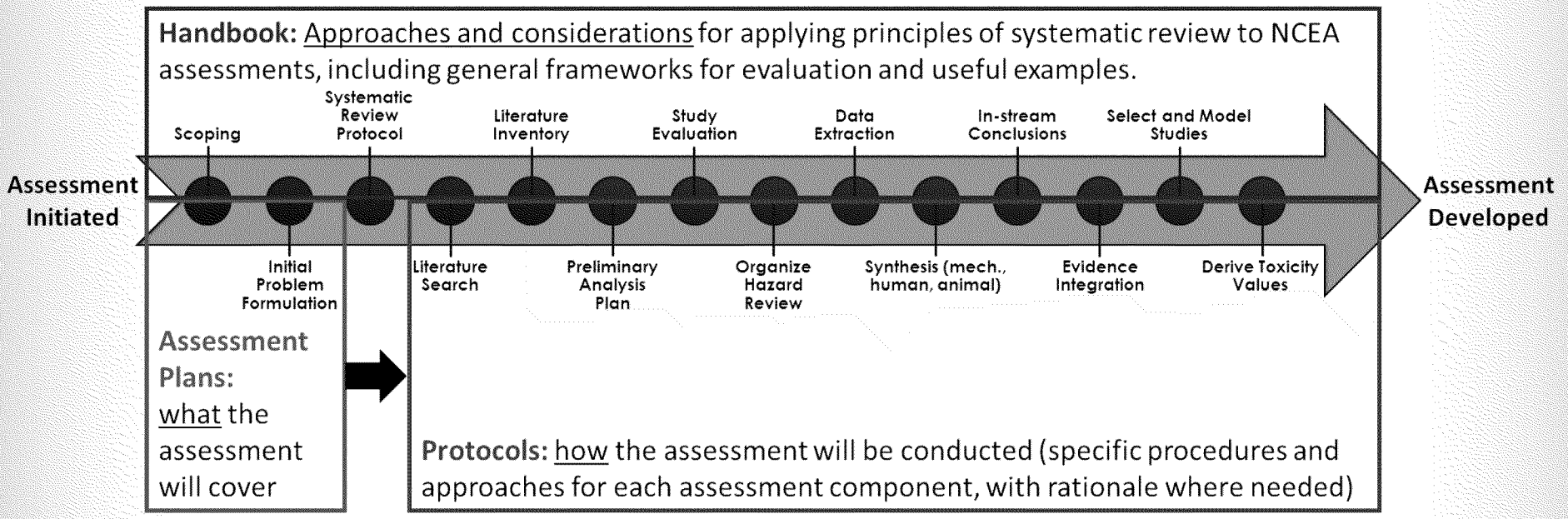
"The committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature." [p.157]

"The committee recognizes that the methods and role of systematic review and meta- analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions." [p.157]

Making Systematic Review Pragmatic and Feasible For IRIS

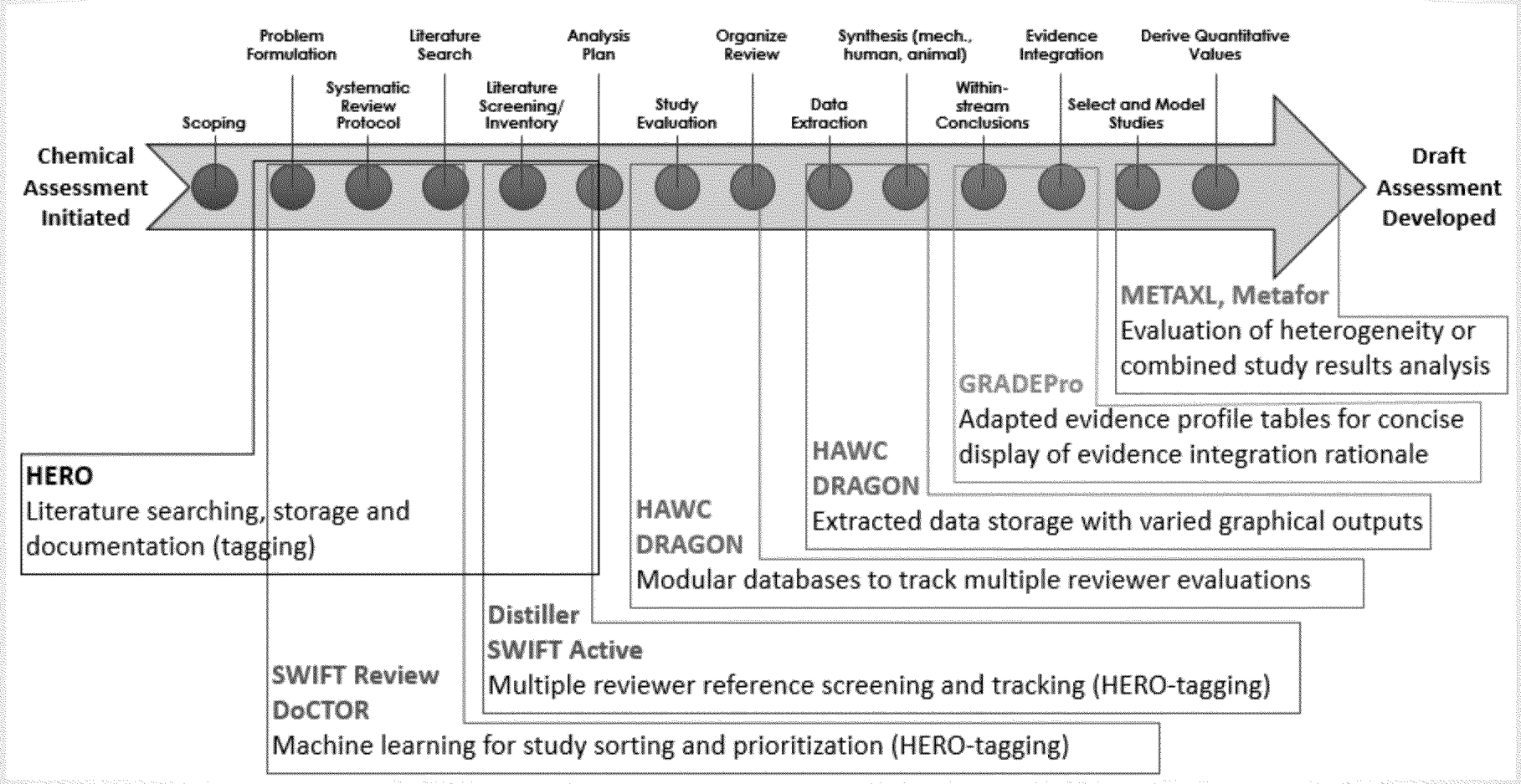
- Standard operating procedures (IRIS Handbook) and chemical-specific protocols
- Use of specialized software applications and automation
- Targeted focus, especially for evidence-rich topics
  - Make better use of well-conducted existing assessments as starting point
- Multiple assessment products ("modularity")
- Solicit early feedback during scoping and problem formulation via assessment plans
  - Summary of scoping and initial problem formulation conclusions, objectives and specific aims of the assessment, draft PECO (Population, Exposure, Comparators, and Outcomes) framework that outlines the evidence considered most pertinent to the assessment, and identification of key areas of scientific complexity
- Utilize iterative protocols to ensure focus on best-available and most-informative evidence as the assessment progresses

Systematic Review Methods



These documents should address previous discussions and suggestions made from during previous SAB reviews related to transparency of literature review and other aspects of the assessment (e.g., ammonia, trimethylbenzenes, ETBE/TBA)

Systematic Review Tools



Tools repository:

HAWC: Data Extraction Animal Bioassay

HAWC

Contact About Public Assessments Your HAWC

Home / Uranium UHA (2017) / Dublineau I et al. 2014 / Create experiment

SELECTED ASSESSMENT x

Uranium UHA (2017)

AVAILABLE MODULES

Literature review
Management dashboard
Study list
Risk of bias
Endpoint list
Visualizations
Executive summary

DOWNLOADS

Download datasets

Create new experiment

Create a new experiment. Each experiment is a associated with a study, and may have one or more collections of animals. For example, one experiment may be a 2-year cancer bioassay, while another multi-generational study. It is possible to create multiple separate experiments within a single study, with different study-designs, durations, or test-species.

Name*

Short-text used to describe the experiment (i.e. 2-year cancer bioassay, 28-day inhalation, etc.).

Type*

Type of study being performed; be as specific as-possible

Chemical name

Chemical identifier (CAS)

CAS number for chemical-tested, if available.

Source of chemical

Chemical purity available?

Purity qualifier

>

Chemical purity (%)

Percentage (ex: 95%)

Chemical vehicle

If a vehicle was used, vehicle common-name

Diet

Description of animal-feed, if relevant

Guideline compliance

Description of any compliance methods used (i.e. use of EPA OECD, NTP, or other guidelines; conducted under GLP guideline conditions, non-GLP but consistent with guideline study, etc.)

Description and animal husbandry

Normal B I U S x_2 x^2

Text description of the experimental protocol used. May also include information such as animal husbandry. Note that dosing regime information

HAWC: Data Extraction Animal Bioassay

HAWC

Contact About Public Assessments Your HAWC

Home / Uranium UHA (2017) / Wade-Gueye et al. 2012 / 9-month drinking water bioassay / Postnatal model, Sprague–Dawley male rats / Create endpoint /

SELECTED ASSESSMENT x

Uranium UHA (2017)

AVAILABLE MODULES

- Literature review
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- Download datasets

Create new endpoint

Create a new endpoint. An endpoint may should describe one measure-of-effect which was measured in the study. It may or may not contain quantitative data.

Endpoint name*

Short-text used to describe the endpoint. Should include observation-time, if multiple endpoints have the same observation time.

System

Relevant biological system

Organ (and tissue)

Relevant organ; also include tissue if relevant

Effect

Effect, using common-vocabulary

Effect subtype

Effect subtype, using common-vocabulary

Additional tags

+

Any additional descriptive-tags used to categorize the outcome

Diagnostic

Diagnostic or method used to measure endpoint (if relevant)

Observation time

Numeric value of the time an observation was reported; optional, should be recorded if the same effect was measured multiple times.

Observation time units*

not-reported

Observation time text

Text for reported observation time (ex: "60-90 PND")

☑ Data reported

Dose-response data for endpoint are available in the literature source

☑ Data extracted

Dose-response data for endpoint are extracted from literature into HAWC

☐ Values estimated

Response values were estimated using a digital ruler or other methods

Dataset type*

Continuous

Variance type*

SD

HAWC: Data Extraction Epidemiology

Contact About Public Assessments Your HAWC

Home / Manganese UHA (2017) / R. M. Bowler et al. 2015 / Create study population

SELECTED ASSESSMENT x

Manganese UHA (2017)

AVAILABLE MODULES

- Literature review
- Management dashboard
- Study list
- Risk of bias
- Endpoint list
- Visualizations
- Executive summary

DOWNLOADS

- Download datasets

Create new study-population

Create a new study population. Each study-population is a associated with an epidemiology study. There may be multiple study populations with a single study, though this is typically unlikely.

Name*

Design*

Age profile

Age profile of population (ex: adults, children, pregnant women, etc.)

Source

Population source (ex: general population, environmental exposure, occupational cohort)

Country*

Region

State

Eligible N

Invited N

Participant N

Inclusion criteria +

Exclusion criteria +

Confounding criteria +

Comments

Note matching criteria, etc.

Save Cancel

Epidemiology: Click to See More Display

"Identifying Research Needs for Assessing Safe Use of High Intakes of Folic Acid"

Draft: Eczema, Prospective Studies

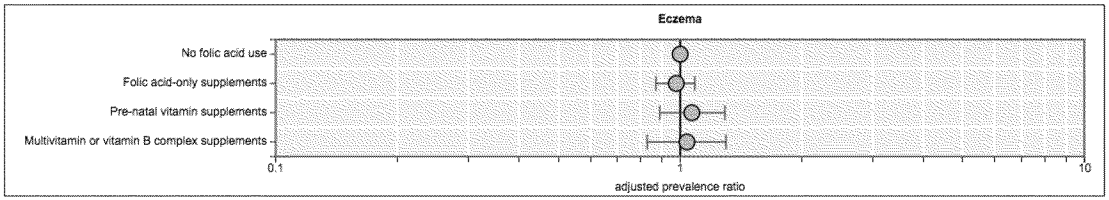
Study	Population Name	Assessed Outcome Name	Exposure Measure	Exposure Comparison Statistical
Bekkers, 2012	PIAMA birth cohort, 1996-1997	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Dunstan, 2012	Pregnant women in Western Australia	Eczema		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until		
Magdelijns, 2011	KOALA Birth Cohort Study	Eczema until		

Bekkers, 2012 / PIAMA birth cohort, 1996-1997 / Folic acid containing supplements during pregnancy / Eczema

Assessed outcome	Eczema
Population description	PIAMA birth cohort, 1996-1997
Diagnostic	self-reported
Diagnostic description	an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles)
Main finding supported?	inconclusive
Prevalence Incidence	0.180 - 0.142, reported by age (Table 2)
Statistical metric presented	adjusted prevalence ratio
Statistical metric description	Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age.
Statistical power sufficient?	not reported or calculated
Dose response trend?	not-applicable
Effect tags	dermal, hypersensitivity, immunological
Adjustment factors	• maternal allergy • maternal education • maternal smoking during pregnancy • number older siblings

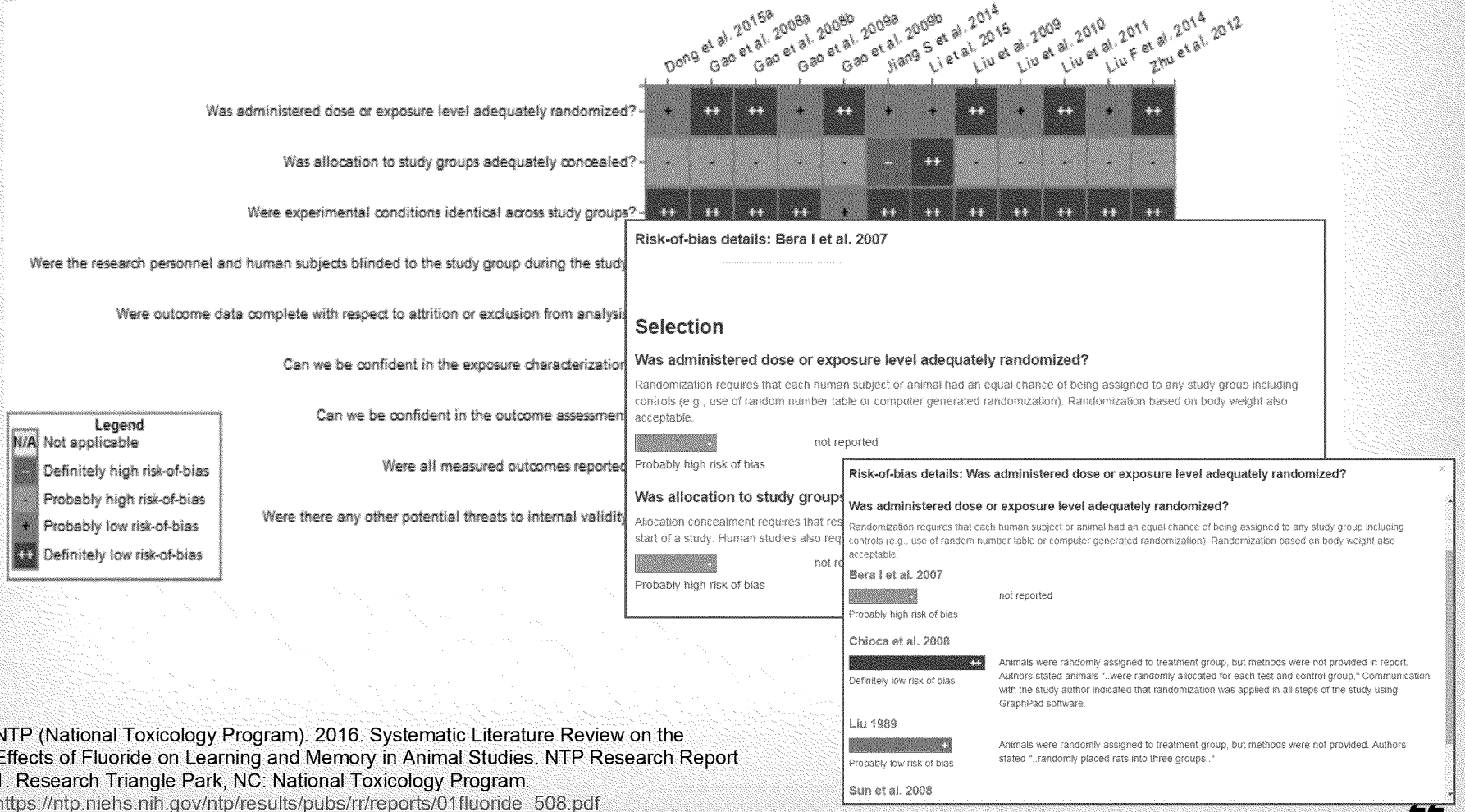
Exposure-group	N	Adjusted prevalence ratio	*p*-value
No folic acid use	1302	1.0	n.s.
Folic acid-only supplements[a]	1998	0.98 (0.87, 1.09)	n.s.
Pre-natal vitamin supplements	287	1.07 (0.89, 1.29)	n.s.
Multivitamin or vitamin B complex supplements	199	1.04 (0.83, 1.3)	n.s.

[a] Main finding as selected by HAWC assessment authors.



NTP Monograph: Identifying Research Need
51. http://ntp.niehs.nih.gov/ntp/ohat/folicacid/final_monograph_508.pdf

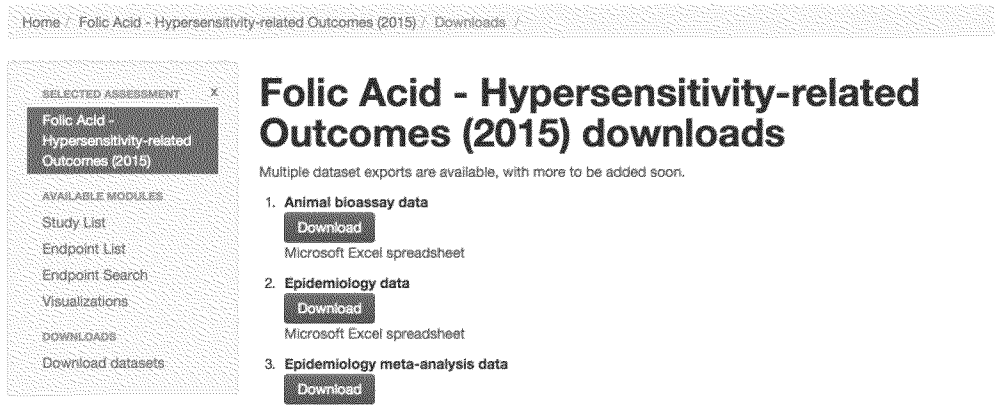
HAWC: Risk of Bias

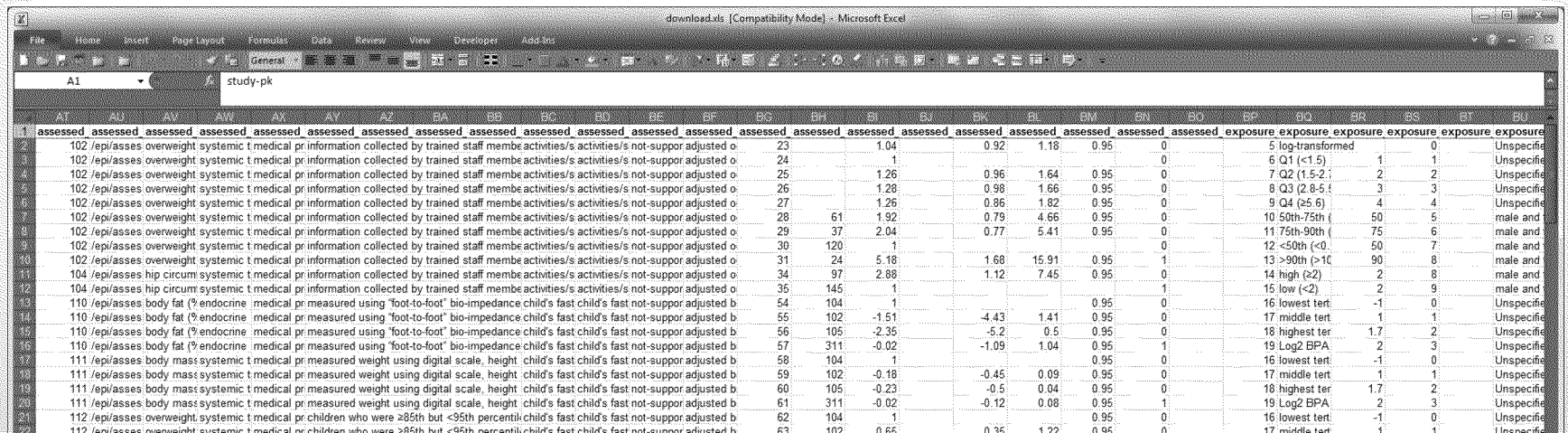


NTP (National Toxicology Program). 2016. Systematic Literature Review on the Effects of Fluoride on Learning and Memory in Animal Studies. NTP Research Report 1. Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/01fluoride_508.pdf

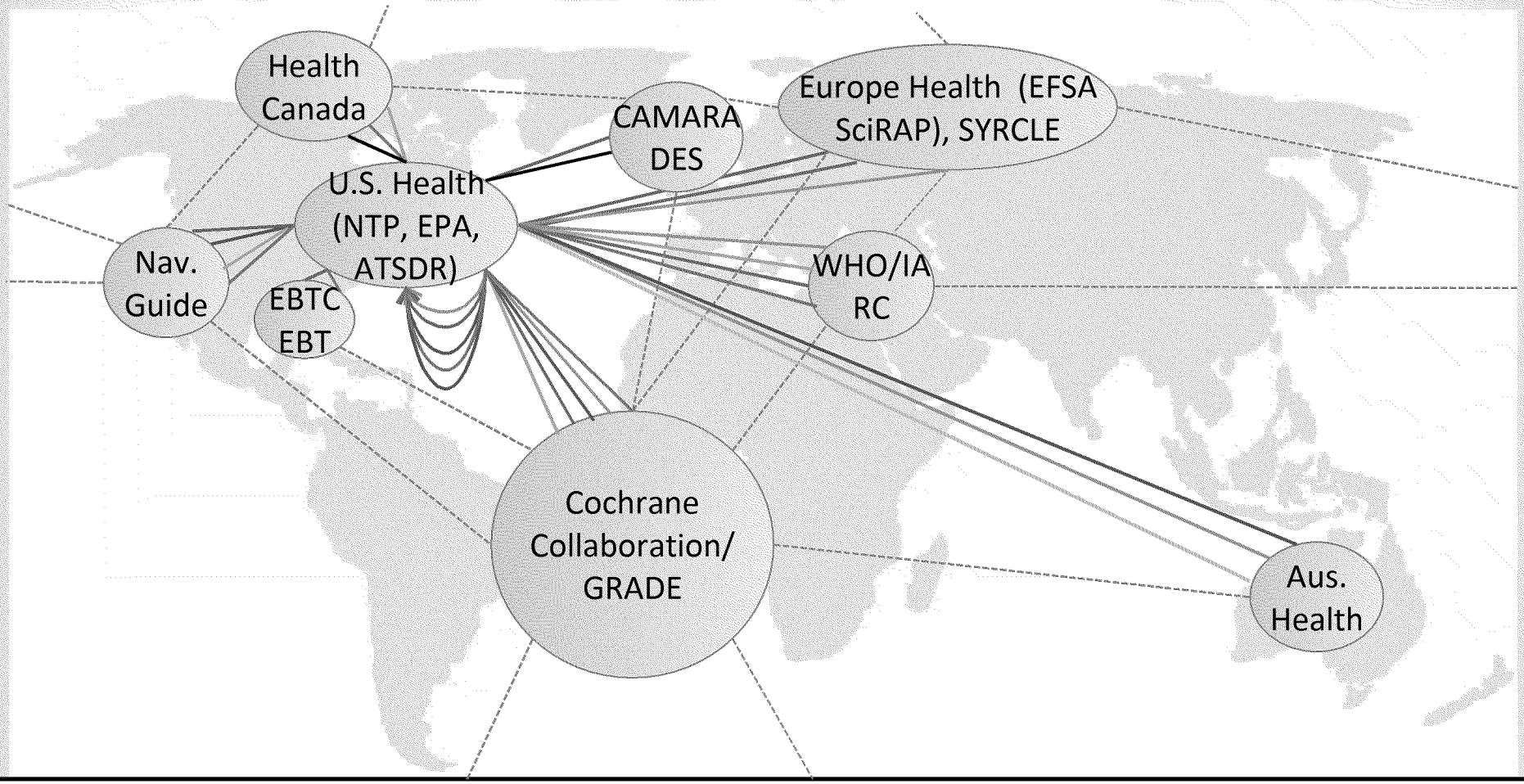
HAWC: Download Reports

- Entire database for an assessment can be downloaded in Microsoft Excel exports





Systematic Review Collaborations in Environmental Health



Known Collaborations (≥ 1)
Sharing Outputs/ Products
Tools (e.g., pilot testing)
Evaluation and Analysis (epi)
Evaluation and Analysis (tox)
Evaluation and Analysis (mech.)
Evidence Integration
Quantitative Approaches
Providing Review/ Feedback

IRIS Multi-Year Agenda

- Developing Agenda
- Released to the public December 2015
- Survey EPA program and regional offices for their assessment needs
- Estimate the resources needed for each assessment by science discipline
- Discuss with senior EPA officials how to meet the most high-priority needs
- Allocation of IRIS resources based on the plan
- Evaluate annually for continued relevance

Group	Chemicals
1	Manganese
	Mercury/methylmercury
	Nitrate/nitrite
	Perfluoroalkyl compounds
	Vanadium and compounds
2	Acetaldehyde
	Ammonia (oral)
	Cadmium and compounds
	Uranium
3	Di-(2-ethylhexyl) phthalate
	Dichlorobenzene isomers
	Methyl t-butyl ether (MTBE)
	Nickel and compounds
	Styrene

September 27-28, 2017 SAB CAAC

Systematic review and implementation within the IRIS Program	**Kris Thayer and Andrew Kraft** *National Center for Environmental Assessment*
Discussion	**Kenneth Ramos and CAAC Members**
Public Comments	**Registered Speakers**

	Assessment Plans and their Role within the IRIS Process	**Jason Fritz** *National Center for Environmental Assessment*
Multi-year agenda group 1 →	**Nitrates/Nitrites**	**Larissa Pardo** *National Center for Environmental Assessment*
Discussed in public during 2014; (re-confirmed as current Agency need) →	**Ethylbenzene**	**Paul Reinhart** *National Center for Environmental Assessment*
Small evidence base (targeted update to address Agency need) →	**Chloroform**	**Ted Berner** *National Center for Environmental Assessment*

***Draft assessment plans for 4 other multi-year agenda group 1 or 2 chemicals planned for 2018 public consultation**

Open Discussion